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Invited commentary

Response to antipsychotic drugs in treatment-resistant schizophrenia: Conclusions based on systematic review



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Schizophrenia affects 1% of general population and one of its features is the heterogeneity of response to treatment. 20–30% of individuals with schizophrenia have treatment-resistant schizophrenia (TRS) (Lieberman, 1999). Correctly identifying these patients could contribute to reduce burden in patients themselves, in society and in economy. In fact, TRS constitutes about 60–70% of schizophrenia's cost burden (Kennedy et al., 2014).

TRS definition was coined by Kane and colleagues in 1988 (Kane et al., 1988). In this groundbreaking trial, they demonstrated superiority in response rate of clozapine over chlorpromazine (30% vs 4%) in well-defined cohort of patients who did not respond to three well documented antipsychotic trials and one prospective trial with high doses of haloperidol. After that, TRS and treatment response concepts have experienced several variations, as analyzed in the review by Suzuki and colleagues (Suzuki et al., 2012), underlining heterogeneity of definitions and proposing consensus definition.

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For these reasons, meta-analyses in this field (Samara et al., 2016; Chakos et al., 2001) could include heterogeneous samples, in part due to unclear or lax TRS definitions. Hence, they are less helpful when searching for evidence based treatment recommendations for TRS (Miyamoto et al., 2015). Another important factors that contribute to this heterogeneity among studies are: dosage differences, investigator bias combined with the difficulty of blinding clozapine treatment assignment, and the effect of prior antipsychotic treatment (Kane and Correll, 2016).

We performed a systematic and critical review of current literature about efficacy of drugs in well-defined TRS. We analyzed key aspects of methodology and quality, definitions of resistance and response, efficacy variables (response rate and mean improvement) and safety outcomes. Here, in this letter, our aim is to present our conclusions about the antipsychotics efficacy and the problems affecting the interpretation of studies on TRS.

Double-blinded randomized trials (DBRT) on TRS were searched by: 1. a systematic search in April 2015 by the following search strategy: schizophrenia[Title] AND (“ultra-resistant”[Title] OR “treatment-refractory”[Title] OR “treatment-resistant”[Title]) AND “English”[Language] from Scopus, PubMed and CINAHL (EBSCO) databases, 2. manual search. We included only studies on treatment efficacy in a clear-defined TRS population according to criteria proposed by Suzuki et al. (2012):

1. History of treatment failure with two or more antipsychotics with different binding profile, clearly documented or prospective validation.
2. Requirement in dose and duration: each treatment with an antipsychotic has continued for six consecutive weeks at chlorpromazine-equivalent doses of ≥ 600 mg/day.
3. Requirement in rating scales: each treatment has resulted in a failure defined with both Clinical Global Impression (CGI) ≥ 4 and Functional Assessment for Comprehensive Treatment of Schizophrenia (FACT-Sz) ≤ 49 or Global Assessment of Functioning (GAF) ≤ 50 or Positive and Negative Syndrome Scale (PANSS) ≥ 75 /Brief Psychiatric Rating Scale (BPRS) ≥ 45 .

Table 1
Double blinded randomized trials about antipsychotic efficacy in treatment-resistant schizophrenia.

Trial	Study description	Compared drugs (mg/d)	Response rate	Completion rate	Improvement of symptoms from baseline	Commentaries
FGA vs FGA						
Lal et al., 2006 (1)	n = 31 15 weeks ITT Inpatients	Levomepromazine (810)/chlorpromazine (760)	53%/42%	90%/73%	– 10/– 7	– No differences in efficacy. – Industry sponsored.
SGA vs FGA						
Kane et al., 2007 (2)	n = 300 6 weeks PP	Aripiprazole (30)/perphenazine (40)	27%/25%	71%/79%	– 10/– 10	– No differences in efficacy. – Missing 116 patients between open-trial and BRDT. – TRS definition was incomplete. – Industry sponsored.
Kane et al., 2006 (3)	n = 306 12 weeks ITT	Ziprasidone (155)/chlorpromazine (740)	58%/55%	90%/88%	NR	– No differences in efficacy. – Unclear results, not reported baseline severity. – Trial conducted in India. – TRS definition was incomplete. – Industry sponsored.
Wirshing et al., 1999 (4)	n = 67 8 weeks PP	Risperidone (7.5)/haloperidol (19)	32%/14%	85%/87%	– 10/– 12	– No differences in efficacy. – Mix TRS and intolerant patients.
Conley et al., 1998 (5)	n = 84 8 weeks ITT and CA Inpatients	Olanzapine (25)/chlorpromazine (1173) + BZT	7%/0%	71%/69%	– 1/+2	– Industry sponsored. – No differences in efficacy. – No industry sponsored.
SGA vs SGA						
Meltzer et al., 2014 (6)	n = 160 24 weeks	RLAI 50/RLAI 100 (biweekly)	45%/45%	72%/70%	– 18/– 18	– No significant differences in efficacy. – Mix TRS patients and poor responders. – Mix SAD and SCZ. – Industry sponsored.
Kane et al., 2011 (7)	n = 321 12 weeks ITT	Risperidone (9)/sertindole (18)	58%/45%	71%/68%	– 21/– 19	– Risperidone had more responders. – Modified version of PANSS. – Lax TRS criteria, unclear selection of participants. – Industry sponsored.
Clozapine vs FGA						
Kane et al., 2001 (8)	n = 71 6 months ITT In- and outpatient	Clozapine (520)/haloperidol (19) + BZT	57%/25%	65%/33%	– 10/– 5	– Clozapine had more efficacy. – Favorable discontinuation rate in clozapine. – Lax response definition. – Industry sponsored.
Hong et al., 1997 (9)	n = 40 12 weeks CA Inpatients	Clozapine (543)/chlorpromazine (1163)	29%/0%	90%/89%	– 8/– 1	– Clozapine had more efficacy. – Conducted in China. – No industry sponsored.
Rosenheck et al., 1997 (10)	n = 423 1 year ITT Inpatients	Clozapine (552)/haloperidol (28) + BZT	37%/32%	57%/28%	– 12/– 8	– No differences in response rate, but favorable discontinuation rate and total improvement in clozapine. – No industry sponsored.
Kane et al., 1988 (11)	n = 268 6 weeks ITT Inpatients	Clozapine (450)/chlorpromazine (900) + BZT	30%/4%	88%/87%	– 16/– 5	– Clozapine had more efficacy. – Industry sponsored.
Clozapine vs SGA						
Sacchetti et al., 2010 (12)	n = 147 18 weeks ITT	Clozapine (365)/ziprasidone (137)	55%/68%	62%/62%	– 24.5/– 25	– Non-inferiority of ziprasidone. – No differences in EPS. – Mix TRS patients and intolerants. – Non-inferiority trial. – Industry sponsored.
Meltzer et al., 2008 (13)	n = 40 24 weeks PP Outpatients	Clozapine (564)/olanzapine (34)	60%/50%	48%/74%	– 20/– 21	– No differences in efficacy. – Mix SAD and SCZ. – High-doses of olanzapine were used. – Industry sponsored.
Tollefson et al., 2001 (14)	n = 180 18 weeks PP In- and outpatients	Clozapine (304)/olanzapine (20.5)	34%/38%	59%/60%	– 14/– 15	– Non-inferiority of olanzapine. – Non-inferiority trial. – Industry sponsored.
Azorin et al., 2001 (15)	n = 273 12 weeks PP In- and outpatients	Clozapine (642)/risperidone (9)	48%/43%	72%/74%	– 23/– 18	– No differences in response rate but clozapine improved more BPRS and CGI. – Industry sponsored.

(continued on next page)

Table 1 (continued)

Trial	Study description	Compared drugs (mg/d)	Response rate	Completion rate	Improvement of symptoms from baseline	Commentaries
Bondolfi et al., 1998 (16)	n = 86 8 weeks ITT Inpatients	Clozapine (300)/Risperidone (6)	65%/67%	79%/79%	–23/–27	– No differences in efficacy. – Mix TRS patients and intolerants. – Industry sponsored.

ITT intention to treat analysis, PP per-protocol analysis, CA completers analysis, BZT benzotropine, SAD schizoaffective disorder, SCZ schizophrenia patients, EPS extra-pyramidal symptoms, TRS treatment-resistant schizophrenia, FGA first-generation antipsychotics, SGA second-generation antipsychotics, RLAI risperidone long-acting injection, NR not reported.

(1) Lal S, Thavundayil JX, Nair NP, Annable L, Ng Ying Kin NM, Gabriel A, Schwartz G. Levomepromazine versus chlorpromazine in treatment-resistant schizophrenia: a double-blind randomized trial. *J Psychiatry Neurosci*. 2006 Jul;31(4):271–9.

(2) Kane JM, Meltzer HY, Carson WH Jr, McQuade RD, Marcus RN, Sanchez R; Aripiprazole Study Group. Aripiprazole for treatment-resistant schizophrenia: results of a multicenter, randomized, double-blind, comparison study versus perphenazine. *J Clin Psychiatry*. 2007 Feb;68(2):213–23.

(3) Kane JM, Khanna S, Rajadhyaksha S, Giller E. Efficacy and tolerability of ziprasidone in patients with treatment-resistant schizophrenia. *Int Clin Psychopharmacol*. 2006 Jan;21(1):21–8.

(4) Wirshing DA, Marshall BD Jr, Green MF, Mintz J, Marder SR, Wirshing WC. Risperidone in treatment-refractory schizophrenia. *Am J Psychiatry*. 1999 Sep;156(9):1374–9.

(5) Conley RR, Tamminga CA, Bartko JJ, Richardson C, Peszke M, Lingle J, Hegerty J, Love R, Gounaris C, Zaremba S. Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. *Am J Psychiatry*. 1998 Jul;155(7):914–20.

(6) Meltzer HY, Lindenmayer JP, Kwentus J, Share DB, Johnson R, Jayathilake K. A six month randomized controlled trial of long acting injectable risperidone 50 and 100 mg in treatment resistant schizophrenia. *Schizophr Res*. 2014 Apr;154(1–3):14–22.

(7) Kane JM, Potkin SG, Daniel DG, Buckley PF. A double-blind, randomized study comparing the efficacy and safety of sertindole and risperidone in patients with treatment-resistant schizophrenia. *J Clin Psychiatry*. 2011 Feb;72(2):194–204.

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(12) Sacchetti E, Galluzzo A, Valsecchi P, Romeo F, Gorini B, Warrington L; MOZART Study Group. Ziprasidone vs clozapine in schizophrenia patients refractory to multiple antipsychotic treatments: the MOZART study. *Schizophr Res*. 2009 Aug;113(1):112–21. Erratum in: *Schizophr Res*. 2010 Aug;121(1–3):281.

(13) Meltzer HY, Bobo WV, Roy A, Jayathilake K, Chen Y, Ertugrul A, Anil Yağcıoğlu AE, Small JG. A randomized, double-blind comparison of clozapine and high-dose olanzapine in treatment-resistant patients with schizophrenia. *J Clin Psychiatry*. 2008 Feb;69(2):274–85.

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We found sixteen efficacy DBRT in TRS (Table 1), that is notably smaller number compared to the last meta-analysis (Samara et al., 2016). Nine compared clozapine versus non-clozapine antipsychotics and seven compared antipsychotics other than clozapine among themselves.

Among the seven non-clozapine trials, there were only two well-designed studies with applicable results:

- Conley et al. (1998): showing no advantage in efficacy of olanzapine over chlorpromazine at 8 weeks (7% and 0% respectively).
- Lal et al. (2006): showing how high-doses of FGAs produce more neurological adverse events and they can be difficult to distinguish from symptoms associated with psychosis. The improvement in participants' psychopathology could be, at least in part, secondary to dose reduction.

The other five trials had many flaws which may lead to erroneous conclusions (i.e. lax TRS criteria, inclusion of intolerants or schizoaffective patients, unclear results presentation).

Results showed clozapine superiority over first-generation antipsychotics (FGA) in three of four well-designed trials with clear TRS definitions. However, clozapine did not demonstrate superiority over second-generation antipsychotics (SGA): in our meta-analytic calculation there was no statistically significant advantage for clozapine in terms of response (OR 0.94 [95% CI: 0.69–1.27]). The analysis included five studies, including in total 339 clozapine and 347 SGA treated patients. There were no sign of heterogeneity ($\chi^2 = 3.57$, $I^2 = 0.0\%$, $p = 0.47$) and no indication of publication bias (Egger's test, $z = -0.24$, $p = 0.999$). Our results may be true finding, or be partly explained by 1) unclear eligibility criteria (i.e. mixing schizophrenia and schizoaffective patients),

2) unclear results presentation, 3) broad TRS definitions mixing intolerant patients. In fact, clozapine vs SGA trials achieved higher response rates compared to clozapine vs FGA trials (see Table 1). Another important issue was the lower clozapine doses in clozapine vs SGA trials. Regarding this, conclusions of meta-analysis by Samara and colleagues are very clear: “the underdosing in industry-funded trials could constitute a serious problem that could have affected the results”. In addition, only few SGA have been compared with clozapine (i.e. ziprasidone, olanzapine, risperidone) and therefore, the efficacy in TRS-population of another SGAs remains unknown (e.g. amisulpride, aripiprazole, sertindole, quetiapine).

Non-clozapine polypharmacy and high-dose treatment in TRS are not supported by evidence. To our knowledge there are no studies in TRS population that compare clozapine monotherapy with non-clozapine polypharmacy, however there are two small open-trials (Kotler et al., 2004; Suzuki et al., 2008) offering discordant results.

Regarding high-dose treatment, there is only one DBRT (Meltzer et al., 2008) comparing high-dose of olanzapine (35 mg/d) versus clozapine (550 mg/d), showing similar response rates at 6 months (50% and 60% respectively). However, this industry supported study excluded patients who did not respond previously to olanzapine. This reveals another problem about inclusion of samples with different severity of treatment-resistance, since the TRS definition does not state exactly how effective antipsychotics should have been tried before clozapine. I.e. the samples with exclusion of patients who had failed trials of olanzapine may be considered less treatment-resistant than samples that have included non-responders to, for example, both olanzapine and risperidone. Underlining this issue, there is NIMH-sponsored study comparing high-dose of olanzapine (50 mg/d) versus clozapine (450 mg/d), that we did not include in the revision because it had a

cross-over design and originally was a safety trial, showing better tolerability and response rate in clozapine (0% vs 30%) (Conley et al., 2003).

In the review we did not include pragmatic studies because usually they applied a more liberal definition of treatment-resistance or they are not double-blinded (e.g. observational studies, population-based register studies, cost-effectiveness trials or open-label effectiveness trials). However, they may provide longitudinal results beyond acute response, they focus in other important outcomes (e.g. quality of life, social functions, discontinuation rate) and they also contribute to enhance our clinical practice. In fact, in many of these studies clozapine was superior to FGA and to SGA (McEvoy et al., 2006).

To summarize, we know surprisingly little about optimal antipsychotic treatment of TRS. However, clozapine remains as the first-line treatment after a failure of two antipsychotic trials according to treatment guidelines (Gaebel et al., 2005; NICE, 2014) and the results of major pragmatic studies. Varying, and broad definitions of TRS and other issues in methodology mentioned earlier in this Letter may cause problems affecting the interpretation of studies. Indeed, meta-analyses of original studies with low quality methods lead to flawed conclusions. Future efforts must ideally focus on 1. well-characterized TRS samples (e.g. description of symptoms that predominate, onset of resistance, earlier used antipsychotics), 2. consensus definition of TRS to facilitate global interpretation and replication of results (e.g. WHO has produced with an expert panel consensus definition for severe asthma and this is something we need for TRS as well), 3. sample sizes even above 300 participants “to have power to clearly show a difference of 20% between groups for binary outcomes” (Sinclair and Adams, 2014), and 4. studies without industry-sponsorship.

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Contributors

C.M. wrote the first draft of the manuscript. E.J. and A.S. managed the literature searches. All authors contributed to and have approved the final manuscript.

Conflict of interest

There are no conflicts of interests to declare.

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